ABBREVIATIONS USED IN TEXT

FDA = Food and Drug Administration
UCSD = University of California, San Diego

reported to cause lymphomas, stomach polyps, growth retardation and death due to hepatic damage.[1,2,4] The compound also has shown mutagenic activity in the Ames test and it causes DNA damage in hamster ovary cells.[3] The use of rhodamine B as a cosmetic additive in the United States is restricted by the FDA. Lipstick cannot contain more than 6% rhodamine B by weight and oral ingestion is limited to 0.75 mg per day.[9] The cookie from case 1 contained more than 130 times this maximum allowed amount. While red urine due to dye or food ingestion is often considered innocuous, the two cases presented here suggest otherwise. The use of food additives in some countries is not as stringently controlled as in the United States.

In neither of the two cases, however, was there any direct evidence to suggest that the symptoms—case 1, flank pain; case 2, seizure—were associated with rhodamine B ingestion. Comparing symptoms with those of previous cases is not possible as this is the first report of human ingestion of rhodamine B. We do not know how widespread is the ingestion of rhodamine B, but the cookies can be easily obtained from bakeries in Tijuana. As to why rhodamine B was used to color bakery goods, one can only speculate. The most likely explanation is its brilliant pink to red color and its fluorescent properties.

Addendum

Since preparation of this manuscript, additional cookies containing rhodamine B were obtained from a store in Tijuana. Apparently this is a continuing problem.

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Treatment of Chronic Myelomonocytic Leukemia

Vincristine and Prednisone Therapy During Symptomatic Phase or After Transformation to Acute Leukemia

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PRIMARY DISORDERS of bone marrow production characterized by varying dysplastic abnormalities have been termed myelodysplastic syndromes. Included among these are refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation and chronic myelomonocytic leukemia.[1,2] Treatment of patients with these disorders has been unsatisfactory, particularly after transformation to a symptomatic phase of disease with or without transformation to acute leukemia. We report here four cases of patients with chronic myelomonocytic leukemia who were symptomatic or whose disorders had changed to acute leukemia and who achieved hematologic remissions after receiving vincristine sulfate and prednisone.

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Methods

Peripheral blood and bone marrow smears were stained with Wright-Giemsa stain according to standard techniques. Histochemical stains were done as previously described.[3] Terminal deoxynucleotidyl transferase (TdT)-positive blood cells were detected using rabbit antibovine TdT (Bethesda Research Laboratories, Gaithersberg, Md),[4] and fluorescence developed with fluorescein-conjugated, goat antirabbit immunoglobulin G. Both positive and negative controls were run with each specimen.

Patient Characteristics and Results of Treatment

The characteristics of four patients seen with chronic myelomonocytic leukemia at the University of California, San Diego (UCSD), Medical Center are summarized in Table 1. All four patients had elevated leukocyte counts and more than 1,000 circulating monocytes per μl. Bone marrows in all patients showed myeloid hyperplasia with varying numbers of monocytes and monocyte precursors. Three patients had palpable spleens. Other supporting laboratory data varied. Patient 1 had bone marrow karyotypic analysis done on three separate occasions, showing only normal metaphases. She underwent marrow transformation to acute leukemia, and histochemical stains were compatible with acute myelomonocytic leukemia. Patient 2 presented with systemic symptoms including fevers, sweats, weight loss and peripheral edema. His serum lactic dehydrogenase (LDH) level was greatly elevated (Table 1), but the peripheral blood differential showed only small numbers of circulating blast cells. Patient 3 also had a transformation of his condition to acute leukemia. Blast

ABBREVIATIONS USED IN TEXT
LDH = lactic dehydrogenase
TdT = terminal deoxynucleotidyl transferase
UCSD = University of California, San Diego

morphology in this patient was consistent with acute monocytic leukemia and a urinary lysozyme level was elevated to 8.1 μg per ml (normal <2.1). TdT was assayed in the peripheral blood of two patients and the bone marrow of a third, and less than 5% positive cells were found.

All patients received therapy with vincristine and prednisone at varying dosages and schedules. Vincristine was given intravenously at doses of 1.0 to 2.0 mg at intervals of one to three weeks. The prednisone dosage varied from 60 to 100 mg a day and was administered for at least five days following vincristine injections. Patient 3 had been previously treated with busulfan, which caused a decrease in his leukocyte count but had no effect on his peripheral cytopenias or organomegaly (Figure 1). In all four patients, the vincristine and prednisone therapy was accompanied by a rapid fall in the circulating leukocyte count, restoration of the leukocyte differential to a normal pattern and abrogation of thrombocytopenia (Figure 1). Variable effects were seen on hemoglobin concentration. In patient 2, systemic symptoms and abnormal chemical values, including LDH and bilirubin, also returned to normal. All three patients with splenomegaly had dramatic reduction in spleen size in response to vincristine and prednisone therapy. In patients 1 and 2 this response was accompanied by resolution of hepatomegaly and patient 3 had dramatic resolution of lymphadenopathy. Representative cases are presented below.

Response durations were 5, 5, 12 and 2+ months, respectively. Toxicity attributed to the drug therapy was minimal. In patient 2, a steroid psychosis developed after his first course of therapy, but he tolerated further therapy at a reduced prednisone dosage without incident. Dosage adjustments in vincristine were required because of symptomatic paresthesias in one patient and elevation of the serum bilirubin level in another.

TABLE 1.—*Characteristics of Patients With Chronic Myelomonocytic Leukemia*

Patient	Age, Sex	Date	Leukocyte Count /μl	Monocytes /μl	Hb grams/dl	Platelet Count /μl	Blasts /μl	TdT	Splenomegaly	LDH U/ml*	Bilirubin mg/ml†
1	59 ♀	3/78 Chronic phase	30,400	1,800	11.1	440,000	0	NT	+1	150	1.8
		8/81 Acute phase	150,000	15,000	8.0	40,000	22,000	NT	+2	440	2.0
2	79 ♂	Chronic phase	19,500	2,700	11.0	37,000	100	Negative	+3	1,500	2.2
3	63 ♂	11/81 Chronic phase	25,600	7,200	13.3	145,000	0	NT	+1	330	1.8
		3/82 Acute phase	194,600	64,000	8.9	70,000	29,100	Negative	+2	500	2.2
4	62 ♀	10/83 Chronic phase	54,000	28,600	3.7	32,000	0	Negative	0	242	0.9

Hb = hemoglobin, LDH = lactic dehydrogenase, NT = not tested, TdT = terminal deoxynucleotidyl transferase

*Normal <180 U/ml.
†Normal <1.5 mg/ml.

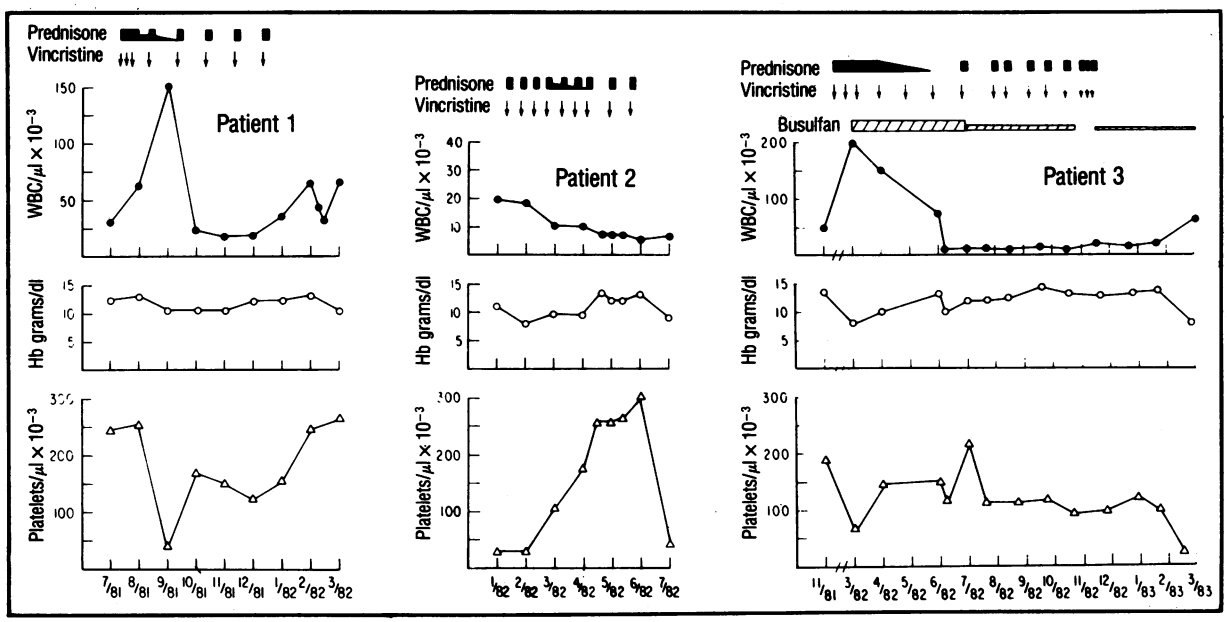

Figure 1.—Effects of vincristine sulfate and prednisone therapy on hematologic values in three patients with chronic myelomonocytic leukemia. WBC = leukocyte count

Reports of Cases

CASE 2. Patient 2, a 79-year-old man, presented in October 1981 to his physician with a two-month history of fatigue, nonproductive cough, fever and night sweats. On physical examination, the patient had 3+ pretibial edema without other signs of congestive heart failure and hepatosplenomegaly. A chest x-ray film was normal. The bone marrow could not be aspirated, but a biopsy specimen showed panmyeloid hyperplasia with abundant megakaryocytes and myeloid forms. Multiple vitamins were prescribed, but the patient's symptoms worsened.

In January 1982 he was seen at the UCSD Medical Center with continued weakness, edema, night sweats and fever. On physical examination, the spleen was palpable 8 cm below the left costal margin and the liver span was enlarged to 18 cm; 2 to 3+ pretibial edema was present. The leukocyte count was 19,500 per μl and the differential 19% polymorphonuclear leukocytes, 7% bands, 1% metamyelocytes, 1% myelocytes, 4% blasts, 15% monocytes, 30% lymphocytes and 23% immature mononuclear cells of uncertain lineage. The LDH level was 1,500 units per ml (normal <180) and total bilirubin 2.2 mg per ml (normal <1.8). A repeat bone marrow study was attempted and again the marrow could not be aspirated. Touch preparations of a biopsy specimen showed erythroid forms with abnormal morphology showing nuclear delay and karyorrhexis. Megakaryocytes were present on the touch preparations and a biopsy specimen, and many showed single, large nuclei. The biopsy specimen showed myeloid hyperplasia with a myeloid-erythroid ratio of 5:1. Reticulin was mildly increased. The patient's peripheral blood contained no TdT-positive cells.

He was treated for one month with a regimen of folic acid, vitamin B_{12} and pyridoxine without response. Treatment with vincristine and prednisone, 60 mg a day (Figure 1), was then begun. The initial dose of vincristine was reduced because of an elevated bilirubin level, but the dose was subsequently 1.5 mg every two to three weeks. The patient experienced a steroid psychosis after five days of prednisone therapy, and this medication was temporarily discontinued. Subsequently he received 40 mg per day of prednisone for five days every two to three weeks and tolerated this well. On this therapy, his leukocyte count returned to normal, his hepatosplenomegaly resolved, his platelet count rose into the normal range and his systemic symptoms abated completely (Figure 1). His edema resolved and his LDH and bilirubin levels returned to normal. He returned to work and remained well until July 1982. Recurrence of systemic symptoms, hepatosplenomegaly and increased LDH and bilirubin values were noted, and his platelet count fell abruptly. He was treated with cytarabine (cytosine arabinoside) without response and died several weeks later. Permission for an autopsy was not obtained.

CASE 4. Patient 4, a 62-year-old woman, presented with a six-week history of anorexia and weakness. She noted a 9-kg (20-lb) weight loss and complained of mild nausea and occasional vomiting. She was referred to the UCSD Medical Center for evaluation. On physicial examination, the patient appeared pale but in no acute distress, without palpable lymph nodes, liver or spleen. The leukocyte count was 54,000 per μl with 19% polymorphonuclear leukocytes, 28% lymphocytes and 53% monocytes. Many of the monocytes were large and had abnormal nuclei with indistinct nucleoli. A subpopulation of the polymorphonuclear leukocytes showed hypersegmentation. The hemoglobin was 3.7 grams per dl and the platelet count 32,000 per μl. A bone marrow biopsy specimen showed a 90% to 95% cellularity with an abnormal number of immature myeloid and monocytic forms. Blasts were less than 5% of the nonerythroid elements. The megakaryocytes showed abnormal morphology; some were small with single, eccentrically placed nuclei and others extremely large with complex nuclei occupying nearly all of the cell. Erythroid precursors showed megaloblastoid maturation and karyorrhexis, but no ringed sideroblasts were present. Immunofluorescent staining for TdT showed no positive marrow cells.

The patient received vincristine, 2 mg given intravenously each week, and prednisone, 60 mg a day, for three weeks. At the end of the first week, her leukocyte count was 1,500 per μl, with 45% polymorphonuclear leukocytes, 51% lymphocytes and 4% monocytes. After transfusion of two units of packed erythrocytes, her hemoglobin was 11.1 grams per dl and the platelet count was 59,000 per μl. After two weeks, her leukocyte count was 8,700 per μl with 27% polymorphonuclear leukocytes, 61% lymphocytes and 12% monocytes. The hemoglobin was 10.9 grams per dl and the platelet count 166,000 per μl. She continues to receive vincristine, 2 mg given intravenously, and prednisone, 60 mg a day for five days every three weeks. Her most recent leukocyte count was 16,300 per μl with a normal differential, her hemoglobin was 10.3 grams per dl and a platelet count was 376,000 per μl.

Discussion

The four cases described in this report conform to previous descriptions of chronic myelomonocytic leukemia.[1,2,5,6] They showed excess proliferation of monocytes and granulocytes, chronic phases of varying duration and hyperplastic bone marrows with ineffective blood cell production in one or more cell lines. Morphologic evidence of dyserythropoiesis, thrombopoiesis or both was present. Two patients had transformation of their disorder to acute monocytic or myelomonocytic leukemia after periods of months to years, a phenomenon well described in cases of chronic myelomonocytic leukemia.[7]

Although descriptions of this disorder,[7] chronic erythromonocytic leukemia,[8] erythromonocytic leukemia[9] and subacute myelomonocytic leukemia [10] have appeared in the past, there have been few reports of effective therapy for these disorders. Various authors have recommended 6-mercaptopurine, methotrexate, hydroxyurea[6] or extremely judicious use of cytarabine or other treatments for acute nonlymphocytic leukemia.[7] Treatment of this rare disorder with any standardized combination chemotherapy regimen has not been reported.

The four patients described here all had dramatic symptomatic improvement and improvement in blood counts after treatment with vincristine and prednisone. Symptomatic remissions were accompanied by regression of organomegaly and normalization of chemical values reflecting organ congestion and ineffective hemopoiesis (LDH). Remissions were seen in two patients with acute leukemic transformations of disease and two symptomatic patients who presented with clinically significant reductions in platelet and erythrocyte counts. Remissions were of short duration (5, 5, 12 and 2+

months, respectively) but contributed substantially to quality of life and were obtained with minimal morbidity.

Previous reports of vincristine-prednisone therapy for cases of monocytic leukemia are difficult to compare with the present series because of changing patterns of treatment of acute leukemia and diagnostic criteria for chronic myelomonocytic leukemia. Geary and co-workers obtained a remission of two years' duration in a symptomatic patient using combinations of cyclophosphamide, vincristine, prednisone, cytarabine, 6-mercaptopurine, thioguanine and daunorubicin hydrochloride.[7] Shaw and Nordquist[11] noted two patients with "pure" monocytic leukemia, one of whom had a "partial remission" and the other a "complete remission" while receiving vincristine and prednisone therapy alone; durations of response were not reported. In our patients, various schedules of administering vincristine and prednisone were used and optimal schedules for drug administration or inclusion of other agents remain undefined. In two patients, symptoms appeared to worsen when intervals between vincristine and prednisone cycles were extended to more than three weeks.

The effectiveness of vincristine and prednisone in a subset of patients with blast transformation of chronic myelocytic leukemia is well documented, and durations of response are similar to those noted in our patients.[12,13] Numerous studies indicate that patients with chronic myelocytic leukemia in transformation whose blast cells contain the enzyme TdT respond to vincristine and prednisone therapy, whereas those whose blasts lack this enzyme seldom respond.[11,12] We did an analysis for TdT in three patients with chronic myelomonocytic leukemia and were unable to show the enzyme in peripheral blood blasts or bone marrow from three patients responsive to the regimen of vincristine and prednisone. Obviously, conclusions regarding the predictive value of TdT in cases of chronic myelomonocytic leukemia cannot be reached using such a small number. These results suggest, however, that TdT may not predict vincristine and prednisone responsiveness in such cases. These drugs provide palliation for symptomatic patients or those with acute blastic transformation. Determining the percent of responsive patients will require larger numbers.

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Minoxidil-Associated Pericarditis and Fatal Cardiac Tamponade

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THE USE OF MINOXIDIL is associated with pericarditis.[1-3] There have been no reports in the literature of hemorrhagic pericarditis caused by minoxidil. We report this case of hemorrhagic pericardial tamponade in a patient receiving minoxidil and heparin to underscore this potential complication.

Report of a Case

The patient, a 70-year-old man with a history of severe hypertension for at least 17 years, had been admitted to hospital in 1971 and 1973 for congestive heart failure attributed to hypertension. Renal insufficiency occurred in the late 1970s with serum creatinine values between 2.5 and 3.5 mg per dl. He never required dialysis. Minoxidil was first used in December 1982 to control his hypertension. His medical regimen at the time of his final admission was furosemide, 40 mg per day; metolazone, 10 mg per day; metoprolol, 25 mg twice a day; clonidine, 0.4 mg twice a day; minoxidil, 10 mg twice a day; nifedipine, 40 mg four times a day; isosorbide dinitrate, 20 mg four times a day; potassium chloride, 40 mEq twice a day, and nitroglycerin sublingually as needed for angina.

His other medical problems included type II diabetes mellitus, hypercholesterolemia and severe diffuse atherosclerotic coronary vascular disease. He had resection of an abdominal aneurysm in February 1981. In June 1982 he had transient right arm and leg weakness for which he refused workup. In January 1983 he experienced a sensory stroke of the right side of the body from which he recovered in one month. An echocardiogram done in April 1983 showed thickened left ventricular walls and a small posterior pericardial effusion. In August 1983 he was admitted because of several hours of sharp left pleuritic chest pain. The pain radiated to the left arm but remained unchanged with different postures. There was no hemoptysis, diaphoresis or nausea.

He appeared apprehensive and in mild distress. Blood pressure was 165/88 mm of mercury with a 15 mm of mercury paradox, pulse was 108 and irregular, respiratory rate 32 and regular and temperature 36.7°C (98°F). Fine rales were present at the lung bases. On cardiac examination he had a 2/6 systolic ejection murmur but no gallop rhythm. No pleural or pericardial rub was appreciated. The jugular venous pressure was estimated at 7 cm of water. An electrocardiogram showed a new onset of atrial fibrillation with a

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